Summary of findings: Ethylene Oxide Carcinogenic Dose-Response Assessment; Development Support Document (DSD) proposed by Texas Commission on Environmental Quality (TCEQ) on June 28, 2019

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I. Summary

TCEQ agreed with EPA that EtO is carcinogenic through a mutagenic mode of action but disagreed with the EPA's data modeling approach. *The TCEQ URF (URE) of 2.5 x 10^{-6} per ppb (1.4 x 10^{-6} per µg/m^3) was derived solely from analysis of lymphoid cancer mortality in men based on the NIOSH cohort.* TCEQ claimed the EPA URE of 9.1 x 10^{-3} per ppb (5.0 x 10^{-3} per µg/m^3; ADAF applied[1]) is too high because the most appropriate model was not used to fit the NIOSH data, and this caused overpredicted mortality. Therefore, TCEQ conducted its own toxicity assessment of the combined NIOSH and UCC cohorts (EPA did not use the UCC cohort data). TCEQ identified Valdez-Flores et al. (2010) as the key study, which analyzed grouped data from the NIOSH (Steenland et al., 2004) and UCC (Swaen et al., 2009) cohorts. TCEQ relied heavily on the Valdez-Flores et al. analysis but derived its own point of departure using a 15-yr lag not adopted in the published study. Notably, TCEQ considered NIOSH breast cancer incidence data, but dismissed it because it was not "scientifically reasonable" for a URF to be below what TCEQ considered endogenous levels. The argument that the EPA's final URE is below endogenous levels was emphasized throughout the DSD in connection with TCEQ's selection of a Cox proportional hazards model of the lymphoid cancer data.

II. Public Comment Period and Peer Review

Initial public comment period deadline was August 12th, 2019. An extension request from Texas environmental groups was granted, extending the deadline to September 26th, 2019. Based on discussion in a May 26th, 2019 meeting, we understand that a letter peer review of the proposed TCEQ DSD is planned (but this is not stated in the DSD or on the TCEQ web site). In the DSD, TCEQ states that a statistician was contracted to confirm accuracy of the analyses. TCEQ guidelines also indicate that the public comment period serves as peer review with the expectation that subject matter experts will choose to comment. Multiple typos of key details (e.g., EPA URE in executive summary) do not instill confidence that this document has received adequate internal review.

[1] EPA URE (no ADAF applied) is 3.0 x 10^{-3} per µg/m^3, which is a more appropriate comparison to TCEQ's derived URF that did not include an ADAF (Note: TCEQ URF is three orders of magnitude lower than the EPA URE).

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III. Primary TCEQ Perspectives: Pros and Cons

Table 1

TCEQ	Pros	Cons	Summary of EPA/SAB response to public comments on this issue
1. The UCC cohort (Valdez-Flores et al., 2010) should be analyzed in combination with the NIOSH cohort to increase power of the statistical analysis of lymphoid cancers (Steenland et al., 2004) [TCEQ 3.2.1.2, p. 13]. *Note: after extensive analysis of the combined and individual cohorts, TCEQ based their final URF on the NIOSH cohort (males only) [TCEQ, p. 67].*	1. Follow-up data on the cohort through 2013 (36.5 years) may provide advantage for predicting long-term effects of EtO exposure (Caveat: this may not be an advantage when considering the healthy worker effect; mortality due to EtO could be masked by overall increased background deaths in an older cohort.) 2. Adding UCC cohort may increase study power for males.	1. Women were not included in the UCC cohort; therefore, breast cancer mortality was not represented. 2. UCC cohort is small ($1/10^{th}$ size of NIOSH cohort with only 27 lymphohematopoietic cancer deaths). 3. Exposures were based on department-specific categorization with few exposure estimates. 4. Coexposures to chlorohydrin introduce confounding (coexposed workers were removed from the analysis). 5. Follow-up 2013 data is unpublished (Bender et al., submitted).	1. While the SAB originally encouraged use of the UCC cohort, the SAB accepted EPA's justifications for excluding it (see cons) and supported using the single NIOSH cohort. [EPA (2016) Appendices K-6 and H-6 to H-8].
2. EPA URE corresponds to EtO exposure lower than endogenous levels estimated at 1.9 ppb by Kirman and Hays (2017) based on a correlation between inhaled EtO and protein adduct formation. The small number of additional protein adducts caused by EtO exposure would be overwhelmed by endogenous adduct levels with no statistical increase in cancer risk [TCEQ 3.4.1.2.1., p. 23].	1. Endogenous EtO likely contributes to background cancer risk. It may be difficult to detect a statistical increase in additional risk due to exogenous EtO exposure that is within the range of endogenous EtO concentrations.	1. The estimated endogenous EtO level is based on a meta-analysis of studies using hemoglobin protein adducts (HEV) as a marker of EtO exposure. The analysis only determined HEV levels in unexposed populations, which was equated to endogenous levels. However, this approach is not equivalent to measuring internally produced EtO levels or associated genetic mutations. 2. EtO is mutagenic and DNA adducts lead to mutations. From an adverse outcome pathway perspective, DNA adducts are a more relevant biomarker of EtO exposure than protein adducts.	1. EPA did not accept this argument stating that ACC calculations (1 ppb) are unrealistic [EPA (2016) Appendix K-9]. 2. EPA cited Marsden et al. (2009) who found an increase in DNA adducts from very low exogenous EtO exposure [EPA (2016), Appendix C-30]. 3. EPA noted that the IRIS risk calculation takes into account background/endogenous EtO levels, and there is no evidence suggesting that low levels of exogenous EtO exposure do not contribute to carcinogenic risk.

TCEQ	Pros	Cons	Summary of EPA/SAB response to public comments on this issue
3. NIOSH breast cancer incidence data as analyzed by EPA should not be considered in the URF derivation because it is "scientifically unreasonable" for excess risk to occur within 1.9 ppb, the mean endogenous EtO level calculated by Kirman and Hays (2017).	None	1. There is strong evidence that EtO causes mammary tumors in animal studies. Excluding the NIOSH breast cancer data based on the argument provided is not scientifically justified.	1. The UCC cohort did not include breast cancer data. Valdez-Flores et al. did not re-analyze the NIOSH breast cancer data stating that it was not publicly available. EPA referenced confidentiality restraints in their response to comments about data accessibility [EPA (2016), Appendix K-2]
4. EPA's choice of a two-piece spline model was not the best fit at low exposures and in the absence of mode of action justification the model should be no more than linear [TCEQ, p. 20]. TCEQ selected a Cox proportional hazards model which gave a sublinear fit of the lymphoid cancer data in the low dose range.	1. The EPA's log-linear model with log cumulative exposure (similar to the Cox model used by TCEQ) had a p-value of 0.02 and good overall statistical fit [EPA (2016), Table 4-6, p. 4-19].	1. This model was considered by EPA but does not fit the low exposure range data. 2. The EPA's version of this model gave a steeper slope in the low-dose region compared to TCEQ's model [EPA (2016), Table 4-6, p. 4-19].	1. The two-piece spline model was selected upon advice from SAB [EPA (2016), Appendix I-9] to best fit low exposure data. A linear Cox regression similar to TCEQ's selected model was also considered but was deemed not the best fit [EPA (2016), p. 4-10].

IV. TCEQ perspectives with timeline of EPA and SAB responses to comments

Overview: All primary arguments challenging the EPA risk calculation that were revisited in the TCEQ DSD have been sufficiently addressed during previous public comment periods according to the SAB (documented in the final EtO IRIS assessment (2016)).

1. Whether to include UCC cohort (Valdez-Flores et al. 1999)

Summary: In their 2007 external review, SAB encouraged EPA to explore use of the UCC cohort (Greenberg and Ott (1990), Teta et al. (1993), Teta et al. (1999)). EPA considered this dataset citing the more recent updates (Swaen et al. (2009) and Valdez-Flores et al. (2010)) and excluded it citing justifications (See Table 1). EPA noted the NIOSH study was more accurate and the best single study based on inclusion of women, use of exposure sampling data and estimated EtO exposure from a regression model, and no co-exposures. Finally, EPA stated it was not possible to combine the NIOSH and UCC cohorts due to differences in study design.

SAB (2007) comments on Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (2006)

- p. 18, line 33: "EPA appropriately identifies Steenland et al. as the critical study for establishing human carcinogenicity."
- p. 18, lines 44-45: "The EPA's reliance on the NIOSH studies in providing a robust basis for assessment is well justified based on the sample size and available quantitative exposure data."
- p. 28, line 28: "The Panel agreed that the NIOSH retrospective cohort study with observations on in excess of 18,000 workers from 13 sterilizing facilities is the best single source of data for determining the dose-response relationship for evaluating the risk of low level EtO exposure in human populations (Steenland et al, 2004)."
    - p. 30, line 32: SAB suggested adding text to clarify why some studies were excluded, for example: "Steenland's dataset was deemed most appropriate because of the larger sample size (n=18,254), gender diversity (45% male, 55% female), lack of potentially confounding co-exposures, and more developed measures of individual worker exposures."
- p. 31, line 5: "To summarize, the Panel concurred that the NIOSH cohort is the best single epidemiological data set with which to study the relationship of cancer mortality to the full range of occupational exposures to EtO. That said, the Panel encouraged the EPA to broadly consider all of the epidemiological data in developing its Draft Assessment. In particular, the Panel encourages the EPA to consider the Greenberg et al. (1990) data on cancer outcomes and EtO exposures for 2174 Union Carbide workers at that firms' two Kana Valley, West Virginia facilities (See Teta et al., 1993; Teta et al., 1999)."
    - *EPA (2011) response to SAB comments, p. 2: "Of the two cohorts with exposure-response data, the NIOSH cohort was used for the quantitative assessment, as it was considered to be substantially superior to the other cohort with respect to a number of key considerations for quantitative risk estimation (in particular, quality of the exposure estimates, cohort size, inclusion of women, and absence of co exposures)."*
    - *EPA (2016) Appendix H-7: "The exposure assessment used by Swaen et al. (2009) for the Union Carbide study was relatively crude, based on just a small number of department-specific (high-, medium-, and low-exposure intensity) and time period-specific (1925–1939, 1940–1956, 1957–1973, and 1974–1988) categories, and with exposure estimates for only a few of the categories derived from actual measurements."*
- p. 31, line 13: "The Panel did not believe that it was necessary to use only one study to arrive at a single potency estimate or to limit the assessment to a single modeling approach. Panel members emphasized that the EPA's own cancer risk assessment guidelines support the consideration of the full range of available data as well as alternatives to the default exposure models."

SAB (2015) Review of EPA's 2014 Revised External Review Draft

- p. 1: "The SAB finds that the National Institute of Occupational Safety and Health (NIOSH) dataset is still the most appropriate dataset to use and concurs with the agency's decision to not use the Union Carbide Corporation cohort data."

2. Consideration of endogenous EtO levels

Summary: In the final report (2016), EPA discussed at length the induction of DNA adducts from endogenous EtO produced from endogenous ethylene. This included discussion of indirect endogenous adduct formation following low concentration EtO exposure (Marsden et al. 2009). They noted human data on adducts and mutations is more limited than animal data. Overall, EPA asserted that the URE represents risk exceeding background risk from endogenous EtO levels.

SAB (2007) comments on Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (2006)

- p. 19, lines 34 – 36: "In order to estimate the increase in cancer risk attributable to a given external exposure, it is clearly important to establish and consider background levels of corresponding DNA damage so that the scale of the incremental increase can be calculated."
    - *EPA (2011) Response to comment, p. 4: "Marsden et al. (2009) support a linear exposure-response relationship for EtO exposure and DNA adducts ($p < 0.05$) and demonstrate increases of DNA adducts from exogenous EtO exposure above those from endogenous EtO for very low exposures to exogenous EtO."*
- p. 19, lines 41 – 44 (into next page): "The Draft Assessment requires a section considering the potential impact of endogenous versus exogenous EtO exposure that carefully lays out (i) why the current evidence of background levels of 2-hydroxyethylation of DNA does not constitute a threshold and (ii) whether the magnitude and variability in endogenous EtO- induced damage may overwhelm any contribution from exogenous EtO exposure (other than some acute high-dose exposure)."
    - *EPA (2011) response to comment, p. 3: "EPA acknowledges that the existence of these high and variable background levels of endogenous EtO-induced DNA damage may make it difficult to observe statistically significant increases in risk from low levels of exogenous exposure, although there is no evidence suggesting that low levels of exogenous EtO exposure do not contribute to carcinogenic risk. Additionally, in a recent study of rats dosed with EtO, Marsden et al. (2009), using sensitive detection techniques and an approach designed to separately quantify endogenous and exogenous N7-(2-hydroxyethyl)guanine adducts, observed increases in exogenous adducts in DNA of the spleen and liver consistent with a linear dose-response relationship. This relationship was observed down to the lowest dose administered, which was a very low dose compared to the LOAELs in the EtO carcinogenicity bioassays."*

SAB (2011) comments citing Marsden et al. (2009)

- p. 20: SAB recommends the following consideration be added to EPA text: "Non-linearities: Are there non-linearities that would suggest that the mutagenic MOA does not continue to be operative at low- or high-dose levels? In the case of EtO, the DNA adduct dose-response extends to very low doses, well below the cancer effect level (Marsden et al., 2009)."
- p. 21: "Inclusion of additional experimental details about the separation of endogenous from exogenous adducts as reported by Marsden et al. (2009) would help provide biological perspective for issues related to risk assessment considerations, especially linearity versus non-linearity of dose- response relationships."

SAB (2015) acknowledgement of EPA response to comments

- SAB summary of EPA response, p. 24: "The EPA concluded that although endogenous EtO is likely to contribute to measurable risk - even significantly more so at low external exposure levels - it is unlikely to overwhelm the effect from external exposure."…. "Based on the discussion presented in the assessment and considering the weight of the evidence from human and animal studies, the SAB finds EPA's conclusion on endogenous exposure to EtO to be supported."
- *p. 31: "Comment #13:* A comment was made from three sources that the EPA should reexamine its risk determination given background and endogenous levels of EtO and that the EPA's risk estimates are unrealistically high. The EPA response explains how background rates for the cancers of interest have been taken into account in the risk determination. They also note that in one of the comments an unrealistic exposure concentration was used in arguing their point. This response is appropriate."

3. Dose-response data analysis and selection of a two-piece linear spline model

Summary: In their 2007 external review, SAB recommended using spline models instead of a Cox linear regression to better fit the data in the low-exposure range. EPA selected a two-piece spline model based on this recommendation. The follow-up comment that the model dose-response should be biologically plausible is confirmed by EPA's response concurred by the SAB's letter to the Administrator.

SAB (2007) comments on Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (2006)

- p. 19, lines 7-9: "There was a strong sense among the Panel that the EPA's risk characterization could be improved by additional analyses of the raw NIOSH data, taking into account the individual exposure data in the dose-response model"
  - *EPA (2011) response to comments: "In addressing breast cancer incidence, EPA was successful in developing an alternative model which is now utilized to estimate the POD for this endpoint. However, alternative modeling approaches did not provide quantitatively stable estimates of risk for the lymphoid cancers."*

- p. 27, lines 5-16: "An EC01 of 44 µg/m3 (0.024 ppm) was calculated using a life-table analysis and linear modeling of the categorical Cox regression analysis results for excess lymphohematopoietic cancer mortality in males reported in a high-quality occupational epidemiologic study (Steenland et al., 2004). Linear low-dose extrapolation from the LEC01 yielded a lifetime extra cancer mortality unit risk estimate of 5.0 × 10-4 per µg/m3 (0.92 per ppm) of continuous EtO exposure. According to EPA's assessment, applying the same linear regression coefficient and life-table analysis to background male lymphohematopoietic cancer incidence rates yielded an EC01 of 24 µg/m3 (0.013 ppm) and a preferred lifetime extra cancer unit risk estimate of 9.0 × 10-4 per µg/m3 (1.6 per ppm). The preferred estimate was greater than the estimate of 5.0 × 10-4 per µg/m3 (0.91 per ppm; EC01 = 44 µg/m3) calculated, using the same approach, from the results of a breast cancer incidence study of the same worker

cohort (Steenland et al., 2003), and was recommended as the potency estimate for Agency use."[2]

- p. 29, lines 31-34: "The final model produced an R^2 to the cross-validation exposure measurements (cross validation sample) of 0.85. There was consensus among the Panel that the exposure model development for the NIOSH data was conducted in a rigorous fashion and it would be difficult to improve on the exposure estimates generated by the NIOSH exposure measurement study (Griefe et al., 1988, Steenland et al., 1987)."

- p. 40, lines 7-12: "...the EPA should carefully consider the scientific justification for a "men only" model for its assessment of the risk of lymphohematopoietic cancer hazards. There should be a strong scientific argument for excluding the female data. Presently, the draft document identifies no basis for excluding the female data. In the data set, women on average have lower average levels of estimated exposure to EtO (possibly more relevant to the exposures of interest in the risk assessment)."
  - *EPA (2013) Appendix H-35: "In the final assessment, the lymphohematopoietic cancer unit risk estimates are based on data for both sexes."*

SAB (2015) comments on Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (2006)

- p. 2: "Specifically, the SAB recommends prioritizing functional forms of the exposure that allow regression models with more local fits in the low exposure range (e.g., spline models)."

- p. 2: "For lymphoid cancer, the draft assessment presents a linear regression of categorical results using dose categories as the preferred model for the derivation of the unit risk estimate for low exposure to EtO. The SAB prefers the use of continuous individual-level exposure data over the use of categorical results. The linear regression of categorical results should not be selected unless the individual exposure model results are biologically implausible."

- p. 14: "The SAB recommends that the linear regression of categorical estimates not be selected unless the individual exposure model results are biologically implausible (for which evidence is not presented in the draft assessment). Instead, the SAB prefers the use of individual-level continuous exposure data. The models developed using individual-level continuous exposure data appear to be appropriate even though the draft assessment states that they are unsuitable. The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures. These are summarized in Figure 4-2. The SAB does not agree with the conclusion that the linear regression of the categorical results is a preferable model over the other, better-fitting models using individual-level exposure data."

  EPA (2016), p. I-4: "In response to SAB comments, the EPA has changed its model selection for lymphoid cancer from the linear regression of categorical results to a model based on individual-level exposure data. The EPA presents unit risk estimates from multiple models for comparison (see Table 4–7) and has updated the justification for

[2] This 2006 analysis is provided as a comparison to the final analysis (underlines added). Note that the 2006 draft used a categorical Cox regression analysis and selected the more sensitive endpoint, lymphohematopoietic cancer, rather than adding risk from both lymphohematopoietic cancer and breast cancer, as was done in the final assessment.

model selection (see Section 4.1.1.2). Consistent with SAB recommendations, the model selection now emphasizes use of the individual-level data, prioritization of functional forms that allow more local fits in the low-exposure range (e.g., spline models), the principle of parsimony, less reliance on AIC, a weighing of biological and statistical considerations, and prioritization of models that can be used for both environmental exposures and the occupational exposure scenarios. As a result of these model selection emphases, the EPA has selected the two-piece linear spline model with the knot at 1,600 ppm × days for the lymphoid cancer data (see Section 4.1.1.2)."

- p. 31: SAB's evaluation of EPA response to public comment: "*Comment #9:* A comment from two sources criticized the EPA for using a non-peer-reviewed supralinear spline model. The response notes that the model was published in 2011. Further, the response notes that use of the model will receive additional review by the SAB. This response is clear and appropriate."

V. References (names of documents available for public download)

[HYPERLINK "https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=1025"] > history > downloads

- EPA (2006): ETOCARCASS-29AUG06.PDF
- SAB (2007): ethylene_oxide_final_review_draft_report_8-30-07.pdf
- EPA (2011): EPA_RESPONSE_TO_COMMENTS_ETO_2011|ASD.PDF
- EPA (2013): CARCINOGENICITY_OF_ETHYLENE_OXIDE_REVISED_DRAFT_2013-APPENDICES.PDF
- SAB (2015): EPA-SAB-15-012+unsigned.pdf
- EPA (2016): EtO Final IRIS Carcinogenicity Assessment_Dec 2016.pdf